35 USC § 112, first paragraph

Claims 10 and 15-18 remain rejected under 35 USC § 112, first paragraph.

The Examiner states:

Applicant argues that (a) NOD mice are an art recognized animal model for human type I diabetes and presents evidence to that effect, (b) there is no reason to believe that blocking the VLA-4/VCAM-1 interaction in humans would not produce results similar to those in NOD mice, (c) Applicant's assertions that administration of anti-VLA-4 antibodies are useful to treat diabetes-prone mice based on adoptive transfer experiments is validated by the Yang et al. reference which discloses experiments in which diabetes-prone mice were administered rat anti-mouse VLA-4 antibodies whereby the onset of diabetes was significantly delayed, and (d) murine monoclonal antibodies have been shown to be therapeutically effective in a number of human settings. The arguments have been noted but have not been found persuasive because, (a) although Applicant presents evidence that the NOD mouse model is an art recognized model of Type I diabetes, it is clear that the cited reference, Bowman et al. on page 115, second column, cautions about the use of the NOD mouse model for extrapolation of therapeutic intervention into human disease because of the differences in the mice and humans, that is, the natural history of IDD development in NOD mice is quite predictable, however, this is not true of humans because of the genetic and environmental heterogeneity associated with the natural history of IDD in humans and that it has thus been difficult clinical investigators to develop diagnostic tools for the early identification of humans destined to develop IDD and further cautions that for these reasons, studies to prevent (delay or inhibit) onset of IDD in NOD mice (which reads on the enablement of the instant claims) must be carefully analyzed for their applicability to therapeutic intervention in human disease, thus it is clear that the data presented in the instant specification cannot be extrapolated to predict human efficacy *in vivo* because it would be impossible to duplicate the saturation of spleen cells with the desired antibodies prior to onset of the disease, and the results of the instant method could not be predicted from the disclosure, (b) Applicant's stated opinion does not appear to be supported by factual data, either in the disclosure or the literature review (c) differences in administration protocols, including concentrations and timing of injection, makes it difficult to compare the results of the cited study with the instant disclosure and further, although it is clear that chronic administration of anti VLA-4 antibodies, starting at birth, on the homeostasis of VLA-4 associated systems cannot be predicted in humans and (d) the issue raised in the instant rejection is not whether murine monoclonal antibodies have been shown to be therapeutically effecting in a number of human settings but rather whether use of the broadly claimed antibody (which reads on the

murine) will function in the method as claimed. Further, it was well known in the art at the time the invention was made that there are problems with murine monoclonal antibodies that render their use unpredictable *in vivo* in humans, that is, that the patient's body mounts an immune response to the murine immunoglobulins which can lead to anaphylaxis or serum sickness and to the neutralization of the administered antibody. Applicant's arguments have not been found persuasive and the rejection is maintained.

The rejection is respectfully traversed. The Bowman et al. reference teaches that the development of IDD is predictable in NOD mice and the treatment can be designed such that it is initiated prior to the occurrence of insulitis (up to 3 weeks of age) or before the onset of the disease (four to eight weeks of age) while such timing is more different in humans do to the genetic and environmental heterogeneity associated with human IDD. None the less, Bowman concludes that "the NOD mouse has provided a model system to study not only the pathogenesis and natural history of a disease that is similar to human IDD, but also a means by which to test intervention protocols that could be used to prevent the disease in humans." Furthermore, as is discussed below, Yang et al. used an anti-VLA-4 antibody to treat NOD mice at both early and late stages of the disease development. Yang et al. provides that "[t]herapeutic treatment with anti-L-selectin after the onset of insulitis from 10 to 14 weeks of age delayed the onset but failed to prevent spontaneous insulin-dependent diabetes mellitus, whereas anti-integrin $\alpha 4$ treatment resulted in a significant and long-lasting suppression of the disease."

The method of the present invention which uses blockers of the VLA-4/VCAM-1 interaction to treat human type I diabetes, has been shown to be effective in NOD mice both prior to the development of insulitis and after the onset of the disease, i.e., after the mice exhibit extensive insulitis. For example, Yang et al. (a copy which was submitted with the Amendment filed on September 4, 1997) teaches that the administration of an anti-VLA-4 antibody (R1-2) was not only effective in preventing the development of IDD in newborn mice (treatment was initiated first day after birth and continued for 4 weeks) but was also effective in reducing the incidence of over diabetes in mice which exhibit extensive insulitis (treatment was initiated in 10 week old mice and continued for 4 weeks). Yang teaches "that integrin $\alpha 4$ mediated lymphocyte adhesion plays an important role during the spontaneous development of IDDM at early and late stages of the disease process." (emphasis added) In addition, there is no indication in the Yang et al. reference that the saturation of spleen cells with the anti-VLA-4 antibody is required for a successful treatment.

Furthermore, contrary to the Examiner's assertion that there are problems with use of murine antibodies and that such therapies are unpredictable, murine monoclonal antibodies have been shown to be therapeutically effective in a number of human settings.

Claims 10, 12-14 and 16-17 remain rejected under 35 USC § 102, first paragraph.

The Examiner states:

> Applicant argues that the rejection is met by deleting "polypeptides and small molecules" from the claims. The argument has been noted but has not been found persuasive because the claims as originally written read on the currently claimed polypeptides and the issues raised in Section 17 are relevant to the specifically recited VCAM and fibronectin polypeptides, that is that, the specification does not address the pharmokinetic properties of VLA-4 binding polypeptides nor their cross reactivity nor the differences between *in vivo* human treatment and animal models in terms of the fate and activity of the polypeptides. Applicant's arguments have not been found persuasive and the rejection is maintained.

The rejection is respectfully traversed. However, in the interest of expediting prosecution, fibronectin polypeptides have been deleted from claim 10 and claim 27 has been canceled. With respect to the anti-VLA-4 antibodies and soluble VCAM-1 polypeptide, the application includes an example in which the administration of anti-VLA-4 antibody (R1-2) significantly inhibited development of the disease in a mammalian NOD mouse model. (see, e.g. 11:36-14-14 of the specification). The specification also disclosed on page 21 that the adoptive transfer experiment described for the antibodies was repeated successfully with the soluble VCAM molecule, i.e., VCAM 2D-IgG. Furthermore, the Yang et al. reference discussed above teaches that the direct administration of an anti-VLA-4 antibody (R1-2) antibody was effective in treating NOD mice.

Claims 10 and 12-18 remain rejected under 35 USC § 112, first paragraph.

The Examiner states:

> Applicant argues that (a) the claims are directed to delaying the onset of diabetes and (b) it seems highly unlikely that all islet cells would already be dead in such individuals. The argument has been noted but has not been found persuasive because (a) Applicant is arguing limitations not found in the claims as presently constituted and (b) Applicant's expressed opinion that it seems highly unlikely that all islet cells would already be

dead does not address the issue raised in the instant rejection, that is, whether or not the instant method would be predictable in a patient wherein the islet cells are damaged. Applicant's arguments have not been found persuasive and the rejection is maintained.

The rejection is respectfully traversed. As is discussed above, and is reiterated herein, Yang et al. teach that the administration of an anti-VLA-4 antibody (R1-2) was effective in both newborn mice and ten week old mice which exhibit extensive insulitis. Thus, contrary to the Examiner's assertion, there is no indication in the art that the presently claimed method would not be successful in patients whose islet cells are damaged.

Claims 10 and 12-18 remain rejected under 35 USC § 112, first paragraph.

The Examiner further states:

Applicant argues that the method of the invention was shown to treat and not exacerbate the diabetes-like condition in NOD mice. The argument has been noted but has not been found persuasive because animal models do not fully mimic the biology of human patients. Further the issue raised in the instant rejection is not whether the method of the invention treated or exacerbated the diabetes-like condition in NOD mice but rather the unpredictability of the effects of the instant method of treatment on perturbation of the complex regulatory networks involving VLA-4 positive cells in humans. Applicant's arguments have not been found persuasive and the rejection is maintained.

The rejection is respectfully traversed. As has been discussed above, and is reiterated herein, the NOD mouse model is the accepted model for human type I diabetes. The Yang et al. reference has demonstrated that the direct administration of an anti-VLA-4 antibody (R1-2) to NOD mice over a four week period did not result in any side effects. See, e.g., page 12606 of Yang et al. which demonstrates that the treatment with anti-VLA-4 antibody did not block the immune responses to self or foreign antigens in NOD mice. Thus, there is no reason to believe that the treatment in humans would have a different effect.

35 USC § 112, second paragraph

Claim 16 remains rejected under 35 USC § 112, second paragraph.

The Examiner states:

> As drawn to improper Markush format of claim 16 Applicant argues that the rejection is met by amending claim 16. The argument has been noted but has not been found persuasive because claim 16 has not been amended to recite "selected from the group consisting or" with the use of the conjunction "and". Applicant's arguments have not been found persuasive and the rejection is maintained.

The rejection is met by amending claim 16.

Double Patenting

Claims 10 and 15-18 remain provisionally rejected under 35 USC § 101 as claiming the same invention as that of claims 10-11, 13, 12-14 and 16 of copending application Serial No. 08/447,098.

The Examiner states:

> Applicant argues that the provisional rejection will be met when claims have been allowed in both applications, thus the rejection is maintained since the claims have not been canceled nor has a terminal disclaimer been filed.

The Applicant respectfully submits that the claims 10-11, 12-14 and 16 of the copending application Serial No. 08/447,098 will be canceled.

35 USC § 112, first paragraph

Claims 10, 12-18 and 25-29 are rejected under 35 USC § 112, first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method for treatment of diabetes comprising administering an antibody, fragment of such antibody, soluble VCAM-1 polypeptides or fibronectin polypeptides.

The Examiner states:

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. The claims as broadly written read on treatment of any and all aspects of diabetes. The specification provides neither guidance on nor exemplification of any aspect of diabetes treatment other than delayed onset of diabetes in a NOD mouse adoptive transfer model. Reasonable correlation must exist between the scope of the claims and the scope of enablement set forth, and it cannot be predicted from the disclosure how or whether the instant method will treat any or all aspects of diabetes. Therefore, undue experimentation would be required to enable the claims.

The rejection is respectfully traversed. The claims are limited to the treatment of type I diabetes. As is discussed above, and is reiterated herein, Yang et al. teach that the administration of an anti-VLA-4 antibody (R1-2) is effective in early and late stages of the disease development in NOD mice. For example, treatment of neonatal NOD mice with R1-2 prevented development of spontaneous IDDM in these mice, while the treatment of 10 week old NOD mice which exhibit extensive insulitis with the same antibody significantly reduced the incidence of overt diabetes in these mice.

35 USC § 112, second paragraph

Claims 10, 12-18 and 25-29 are rejected under 35 USC § 112, second paragraph.

> The Examiner further states:
> Claims 10, 12-18 and 25-29 are rejected under 35 USC § 112, second paragraph because claim 10 recites the "a method of treatment. . . effective to treat diabetes. The claim is confusing because it is not clear what treatment is being effected, for example, is the output of insulin increased, is the onset of the disease being delayed?

The rejection is respectfully traversed. The arguments made above in response to the 35 USC § 112, first paragraph rejection are reiterated herein.

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CONCLUSION

Amendments and cancellations of the claims are to expedite prosecution and should not be construed as acquiescence to or agreement with the Examiner's rejections. Applicant reserves the option to further prosecute the same or similar claims in the present or in another patent application.

In view of the above, Applicant submits that the claims are in condition for allowance and requests such action. Please apply any charges not covered, or any credits, to Deposit Account 12-0080.

Respectfully submitted,

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